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Review

Advantages of nonhuman primates as preclinical models for evaluating stem cell-based therapies for Parkinson's disease

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ABSTRACT

The derivation of dopaminergic neurons from induced pluripotent stem cells brings new hope for a patient-specific, stem cell-based replacement therapy to treat Parkinson's disease (PD) and related neurodegenerative diseases; and this novel cell-based approach has already proven effective in animal models. However, there are several aspects of this procedure that have yet to be optimized to the extent required for translation to an optimal cell-based transplantation protocol in humans. These challenges include pinpointing the optimal graft location, appropriately scaling up the graft volume, and minimizing the risk of chronic immune rejection, among others. To advance this procedure to the clinic, it is imperative that a model that accurately and fully recapitulates characteristics most pertinent to a cell-based transplantation to the human brain is used to optimize key technical aspects of the procedure. Nonhuman primates mimic humans in multiple ways including similarities in genomics, neuroanatomy, neurophysiology, immunogenetics, and age-related changes in immune function. These characteristics are critical to the establishment of a relevant model in which to conduct preclinical studies to optimize the efficacy and safety of cell-based therapeutic approaches to the treatment of PD. Here we review previous studies in rodent models, and emphasize additional advantages afforded by nonhuman primate models in general, and the baboon model in particular, for preclinical optimization of cell-based therapeutic approaches to the treatment of PD and other neurodegenerative diseases. We outline current unresolved challenges to the successful application of stem cell therapies in humans and propose that the baboon model in particular affords a number of traits that render it most useful for preclinical studies designed to overcome these challenges.

Contents

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1. Introduction

PD is a neurodegenerative disorder characterized by the selective loss of dopamine-producing neurons in the substantia nigra pars compacta (SNc) (Carlsson, 1959; Ferri et al., 2007). Rigidity, postural instability, bradykinesia, and resting tremor are the cardinal symptoms (Parkinson, 1817; Dauer et al., 2002), but 50–80% of patients with PD also suffer cognitive impairments such as dementia (Litvan et al., 2012; Hely et al., 2008), personality changes including depression, anxiety, and passivity (Fahn, 2010), and other non-motor symptoms such as sleep irregularity, incontinence, constipation, and fatigue, which typically persist despite treatment (Chaudhuri and Quinn, 2006). Symptoms emerge when approximately 50–60% of the SNc neurons are lost, corresponding to an 80–85% deficit in dopamine levels within the striatum (Wirdefeldt et al., 2011). By the time of death, typically 70–90% of the SNc neurons have been lost (Davie, 2008; Bernheimer et al., 1973; Riederer and Wuketich, 1976).

There are no curative agents for PD, and all available treatments target only the symptoms of the disease. Stem-cell based therapies represent a novel and promising approach to mitigate this disease, however the efficacy and safety of this approach must be optimized prior to its introduction into the clinic including the use of relevant animal models. Due to their close phylogenetic proximity to humans, nonhuman primates (NHPs) provide the most accurate models for such preclinical studies. Of particular relevance to transplantation of stem cell-derived neurons into the brain for the treatment of Parkinson's disease (PD), NHPs accurately mimic key neuroanatomical, neurophysiological, immunological, and genetic features of humans. Among NHP species available for use in biomedical research, the baboon offers several specific characteristics that render it the most promising NHP model for studies of cell-based therapies for PD.

Currently, dopamine replacement therapy is the most common treatment for PD (Tarsy, 2015). The immediate precursor to dopamine, L-dopa, is administered to patients because dopamine itself is incapable of crossing the blood brain barrier (Carlsson, 1959). However, L-dopa induces dyskinesia (Calabresi et al., 2010), increased coronary artery disease (Rogers et al., 2003), emesis in humans (Tarsy, 2015; Bieger et al., 1977; Sanger and Andrews, 2006), and some suggest it accelerates neuronal degeneration (Parkinson Study, 2000; Whone et al., 2003; Group, 2002). More recently, deep brain stimulation of the subthalamic nucleus, globus pallidus, or pedunculopontine nucleus has been used to treat PD (Kumar et al., 1998; Stefani et al., 2007). While deep brain stimulation has proven effective for eliminating some of the motor symptoms of PD, it has shown limited capacity to reduce non-motor symptoms (Fasano et al., 2012). It also does not effectively treat axial motor deficits such as postural instability, and the efficacy of deep brain stimulation declines as the disease progresses (Kleiner-Fisman et al., 2003).

As an alternative to dopamine replacement therapy and deep brain stimulation, PD may be treated by replacing lost neurons with neural tissue derived from progenitor cells. Prior to the advent of pluripotent stem cells, clinicians attempted to treat PD by transplanting cells derived from a variety of heterologous tissue sources into the striatum (Bjorklund and Kordower, 2013). Fetal ventral mesencephalon tissue demonstrated the most success in preclinical studies in rodents, but ultimately failed to significantly reduce parkinsonism in double-blind clinical trials (Freed et al., 2001, 2011; Olanow et al., 2003). There are at least three factors potentially culpable for the failure of previous human clinical trials of cell-based transplantation therapy for PD: 1.) the use of a heterogeneous cell population as a tissue source, 2.) transplanting tissue to a heterotopic graft site, and 3.) the lack of an optimized immunosuppressive regimen (Bjorklund and Kordower, 2013; Lindvall, 2013).

The discovery of pluripotent stem (iPS) cells, which are derived from a patient's own cells, provided an avenue to potentially mitigate immune rejection while simultaneously circumventing the ethical hindrances of using tissues from aborted fetuses. There are a number of studies reporting the ability to differentiate iPS cells into dopamine neurons and subsequently transplant those neurons into rodent brains (Xi et al., 2012; Morizane et al., 2013; Sundberg et al., 2013; Hallett et al., 2015). Although these studies used tissues derived from the host, results demonstrating tolerance of the grafts by the host immune systems are inconsistent (Morizane et al., 2013; Hallett et al., 2015; Soldner et al., 2011; Guha et al., 2013; Araki et al., 2013; Kaneko and Yamanaka, 2013; Kruse et al., 2015; Itakura et al., 2015; Xian and Huang, 2015). Further, as mouse models of PD typically do not display non-motor symptoms (Table 1), these studies were unable to test the ability of stem cell-derived tissue grafts to treat all deficits associated with the disease. Nevertheless, these studies did demonstrate that an autologous dopamine neuron graft is capable of significantly reducing the motor defects in rodents whose midbrain dopamine neurons had been genetically or pharmacologically lesioned.

More recently, work has been performed in the NHP species, *Macaca fasicularis* (the crab-eating macaque), in which autologously transplanted iPS-derived dopamine neurons were able to survive and restore motor deficits for up to 2 years (Hallett et al., 2015). However, the degree to which studies investigating immune tolerance in *Macaca fasicularis* are able to accurately predict outcomes in humans remains a question (see Section 3 of this review). Further, while some non-human primate species have been shown to display non-motor symptoms after MPTP treatment (Hantraye et al., 1996), the ability for iPSC-derived tissue grafts to restore the non-motor deficits in MPTP treated monkeys remains untested. Therefore, questions still remain as to the safety and efficacy of cell-based therapies for PD. Clinical trials have not yet been attempted in humans (Freed et al., 2011), but the inconsistent results of animal studies conducted to date exemplify the need for further, more informative NHP preclinical studies to optimize the safety and efficacy of cell-based therapies for PD.

The possibility of a cell-based replacement approach based on derivation of patient-specific iPS cells (Takahashi et al., 2007) and the subsequent directed differentiation of these cells into transplantable dopaminergic neurons (Soldner et al., 2009) has engendered renewed optimism that an effective cell-based treatment for PD can be developed. iPS cells circumvent the ethical impediments that accompany the use of tissues derived from aborted fetuses (Freed et al., 2001; Olanow et al., 2003, 1996), or from human embryos as would be required for an embryonic stem cell based approach (McHugh, 2004). However, several technical issues surrounding the development of an optimal cell-based protocol for the treatment of PD remain largely unresolved, including 1.) the determination of an optimal target graft site, 2.) the identification and purification of the appropriate neuronal subtype to be transplanted, and 3.) determination of an optimal immunosuppressive regimen necessary to the extent needed to support an autologous transplantation approach. Additionally, long-term studies must be conducted to interrogate both the immunogenic and tumorigenic potentials of the transplanted cells, as well as to assess the full range of therapeutic

Table 1
Comparison of key features of a transplantation model for Parkinson's disease.

	Rodent		New World Monkey	Old world monkey		Hominidae
	Mouse	Rat	Marmoset	Macaque	Baboon	Human
Genome identity with humans	48–66%[46, 47]	44–64%[46, 47]		92%[48]	92%[49]	100%
MHC class I sequence identity with humans			82%[167]	90–99%[171]	90–99%[173]	100%
Physical separation of caudate and putamen	No	No	Yes	Yes	Yes	Yes
SNc TH+ neurons (×10^3)		12.7[60]–15.7[59]	29.9[60]	203[60]	259[60]	382[60]
Grey matter to white matter ratio	11.22[121]	6.38[121]	3.16[121]	1.91(121)	1.083[121, 289]	3.0 (young)–1.0 (aged)[290](121)
Midbrain response to aversive stimuli	VTA responds[98]	VTA responds[291]		VTA and SNc respond[96, 196]		VTA[292] and SNc[293] respond
IgG subclasses	I, IIA, IIB[294]	I, IIa, IIb, IIc[295]		I,II, IV[185]	I, II, III, IV[185]	I, II, III, IV(185)
Relationship of IL–1 levels with age	+[296]	+‡[297, 298]		No assoc.[201]		+[195, 196]
Relationship of IL–6 levels with age	–[299, 300]			–[201]	+[204]	+[193]
Relationship of IL–8 levels with age	–[301, 302]		No assoc.[200]			+[194]
Relationship of IL–10 levels with age	+[303]			+[201]	No assoc.[204]	+[195](196)
Relationship of C–reactive peptide levels with age			No Assoc.[200]		+[204]	+[193]
Relationship of TNF–α levels with age	–[299, 300]	+[298]		–[201]	+[204]	+[195, 196]
Relationship of TGF–ß1 levels with age	+†[297]	+[304]			–[205]	–[197]
Relationship of DHEA levels with age		–[305]			–[205]	–(198)
MPTP sensitivity	Insensitive[228]	Insensitive[229]	Sensitive[240]	Sensitive[241]	Sensitive	Sensitive[243]
MPTP impairments	H/B, T[306]	H/B, T[307]C[308]	H/B R, T, P, C[265]	H/B R, T, P, C[249]	H/B[256]R[256], T[256], P[257], C[41]	H/B R, T, P, C[259]

Dissimilar From Human

Similar to Human

† mRNA was elevated, protein status is unknown.

‡detected elevated IL–1 in rat hippocampus and spleen with age but nowhere else in the brain nor in serum

H/B= hypokinesia/bradykinesia

R= Rigidity

T= Tremor

P= Postural Instability

C= Cognitive Impairment

benefits accruing from optimized cell grafts (i.e. the improvement of non-motor deficits).

Several advantages of NHPs as a preclinical model emerge as one examines the consequences of the evolutionary proximity of NHPs to humans. For example, mice and rats share only 66% (M. G. S. Consortium, 2002) and 64% (Nature, 2004) genome identity with humans, respectively. Macaques (Caccone and Powell, 1989) and baboons (Rogers and Hixson, 1997), on the other hand, both share 92% genome sequence identity with humans (Table 1). NHPs also share significant neuroanatomical similarities with humans, a characteristic that is particularly germane to the identification of an optimal target graft site. Additionally, similarities between the immunogenetics and age-related changes in immune function found in humans and NHPs afford relevance to the use of NHP models for testing potential immune rejection and/or potential tumorigenic outcomes following cell transplants. Finally, the longevity and cognitive abilities of NHPs are much more similar to those found in humans than are those found in rodent species, and this is critical for accurate assessments of the capacity of cell-based therapies to provide long-term relief from both the motor and non-motor symptoms of PD.

The great apes (chimpanzees, gorillas, orangutans) share the greatest genetic similarity with humans (Bontrop and Watkins, 2005), a similar brain volume and organization, and an 86% sequence identity in the major histocompatibility complex (MHC) class I coding region

(Kelley et al., 2005). However, the United States National Institutes of Health has announced that the use of chimpanzees in biomedical research is being abated (Cohen, 2007; Kaiser, 2013). Therefore, we present here a discussion of the most common and most relevant preclinical models excluding the great apes. We review studies performed with the use of rodents and describe advantages of NHPs in general and baboons in particular in regard to the neuroanatomical and neurophysiological characteristics (Section 2), immune system biology (Section 3), and motor and non-motor manifestations of the MPTP lesion (Section 4) needed to validate translation of a stem cell transplantation therapy for PD to the clinic. We conclude that NHP models afford unique advantages over rodent models that are critically important for the accurate recapitulation of the PD disease state and optimization of the efficacy and safety of cell-based approaches to treatment of this disease. Finally, we propose that among available NHP models, the baboon provides the most accurate representation of human conditions relevant to the treatment of PD (Section 5).

2. The NHP for transplantation therapy: addressing the graft location

An important aspect of successful cell transplantation therapy for PD is the restoration of the complete physiological neuronal network (Gaillard and Jaber, 2011; Shinoyama et al., 2013). The standard protocol for transplanting dopamine neurons into a PD model involves grafting new neurons into the striatum, a heterotopic graft location (Laguna Goya et al., 2008). New dopamine cells grafted into the striatum lack the inputs that their physiological endogenous counterparts receive. Accordingly, it is possible that heterotopic transplantation of dopamine neurons may fail to restore behavioral defects that arise due to a dopamine deficit in areas outside the striatum. As opposed to striatal grafts, homotopic grafts into the SNc could be optimally positioned to receive physiological signaling. However, it is unknown to what extent these new axons will be capable of projecting through the adult human brain, to what extent such a graft will be capable of surviving long-term in the SNc, or to what extent homotopic grafts will be capable of restoring striatal and extrastriatal dopamine deficits. When considering the graft location, preclinical studies must weigh these factors against the potential absence of these signaling inputs and how that absence may affect the behavior of dopamine neurons and ultimately, the behavior of the animal. These and other neuroanatomical and neurophysiological similarities shared by NHPs and humans render NHPs the optimal available models for analyzing the relative efficacy of different putative target graft sites. In this section, we review the specific efferent connections of the SNc in rodents (2.1) and NHPs (2.2). We also examine similarities and differences among rodents, NHPs, and humans in electrophysiological properties (2.3 and 2.4), such as neuronal firing rate and response to rewarding or aversive stimuli (2.4 and 2.6). In 2.7, we discuss the advantages and disadvantages of homotopically and ectopically located transplant sites, and propose that the baboon is best suited to test the efficacy of various transplant locations based on its particular set of neuroanatomical and neurophysiological characteristics.

2.1. SNc efferents in rodents

In rodents, efferents of the SNc innervate the striatum (Roeper, 2013). Leaving the SNc, they follow the median forebrain bundle rostrally until they penetrate the dense white matter tract known as the internal capsule. At this point, the fibers either ascend around the perimeter of the dorsal pallidum, descend around the ventral pallidum, or enter the ventral pallidum directly and cut across it *en route* to the putamen, climbing the striatalfugal Wilson's Pencils. Dopaminergic projections to the globus pallidus, subthalamic nucleus, substantia nigra pars reticulata and the prefrontal cortex originate primarily in the VTA or retrorubral field (Roeper, 2013). Therefore, in the rodent, geographical borders delineate dopamine neuron nuclei in the ventral midbrain with each nucleus containing within it neurons that share similar hodology (specific pathways and connections within the neuroanatomical circuit) and immunoreactivity.

2.2. SNc efferents in NHPs and humans

Organization of the primate midbrain differs from that of the rodent. One considerable difference is the disproportionate expansion in the number of dopamine cells in the primate SNc (Duzel et al., 2009). The rat SNc contains up to 15×10^3 TH^+ neurons (Nair-Roberts et al., 2008; Hardman et al., 2002), whereas the marmoset has twice that amount and the macaque has up to 203×10^3 TH^+ neurons (Hardman et al., 2002). Baboons, which have up to 260×10^3 TH^+ neurons in the SNc, are the closest old world NHP to humans (Hardman et al., 2002), which have up to 382×10^3 TH^+ neurons in the SNc (Hardman et al., 2002) (Table 1). These disparities in the number of TH^+ neurons between species are disproportionate in that they cannot be accounted for by linear correlation with overall brain size, and therefore may partially explain why it has been challenging to restore motor functions with stem cell grafts in patients with PD or in NHP PD models when cell-based treatments have produced encouraging results in rodent models (Sanchez-Pernaute et al., 2008; Kriks et al., 2011; Hargus et al., 2010; Thompson et al., 2009; Grealish et al., 2010, 2014. Also unlike rodents, primates show no geographic boundaries that contain within them a group of midbrain dopamine neurons that share hodological, and immunoreactive characteristics (Lynd-Balta and Haber, 1994; Joel and Weiner, 2000). In addition, the primate striatum is split by the internal capsule into the caudate nucleus and the putamen (Fig. 1A–E). Thus, in addition to the striatal connections mentioned above, some SNc efferent fibers do not penetrate the internal capsule in the primate brain, but instead project rostrally through the medial forebrain bundle until they reach the reticular nucleus of the thalamus, which they follow as they extend to their destination in the caudate nucleus (Prensa et al., 2000).

Perhaps one of the most striking neuroanatomical features of primates is the enhanced presence of extrastriatal innervation from the SNc. In both NHPs (Bjorklund and Dunnett, 2007; Mark Williams and Goldman-Rakic, 1998) and humans (Prensa et al., 2000; Björklund and Dunnett, 2007), the SNc projects to structures other than the striatum (Duzel et al., 2009) (Fig. 2), such as the globus pallidus (Smith et al., 1989; Parent et al., 1990), the subthalamic nucleus (Lewis et al., 1988), and the prefrontal cortex (Sharman et al., 2000). Specifically, efferents from the SNc to the dorsolateral frontal cortex may be unique to primates (Mark Williams and Goldman-Rakic, 1998) (Fig. 2). As a result, NHP models of PD and humans with PD may display consequences of dopamine depletion in the extrastriatal structures that are not observed in rodents. For example, type D2 dopamine receptors are prominent in the frontal cortex of humans (Joyce et al., 1991; Murray et al., 1994) and loss of dopamine in this region may result in cognitive deficits in humans (Diamond and Baddeley, 1996). The frontal cortex receives dopamine primarily from the VTA in rodents (Roeper, 2013), and thus dopamine supply to this area may be relatively intact in rodent models of PD, whereas in primates both the SNc and the VTA supply dopamine to the frontal cortex (Duzel et al., 2009). To date, it is not known whether there is a PD-mediated dopamine deficit in the frontal cortex of PD patients, and/or how that deficit might be involved in PD symptoms such as cognitive decline. Further, neurons in the external globus pallidus (GPe), internal globus pallidus (GPi), and subthalamic nucleus (STN) also express dopamine receptors and respond to dopamine agonists and antagonists in humans (Murray et al., 1994).

The exigent nature of extrastriatal dopamine was demonstrated in a study of rhesus monkeys, in which all MPTP-lesioned monkeys exhibited striatal dopamine depletion, but only those that also displayed extrastriatal dopamine depletion presented with parkinsonism (Pifl et al., 1990). Further, it has been demonstrated in humans that

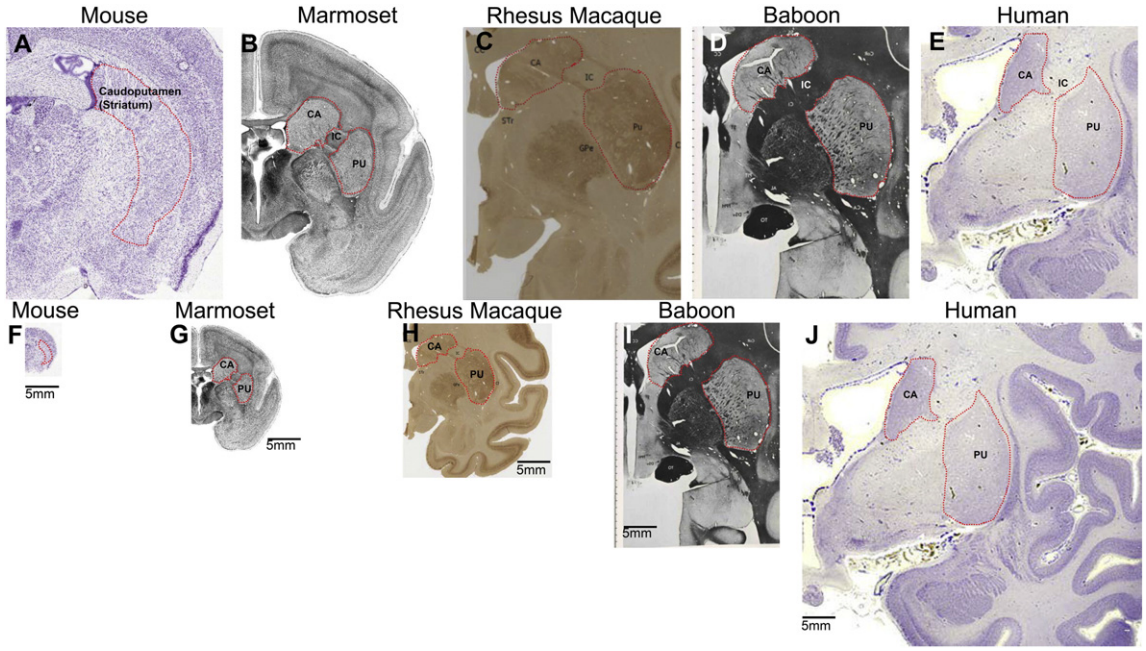

Fig. 1. Comparative anatomy of the putamen and caudate nucleus. A. In the rodent, the putamen (PU) and caudate nucleus (CA), the primary targets of SNc dopamine neurons, are physically merged and therefore indistinguishable (caudoputamen; outlined in red). B–E. In primates, the fibers of the internal capsule (IC) split the CA and PU (outlined in red) into two separate structures. F–J. Coronal views of the basal ganglia, all aligned to the same scale to allow direct comparisons of the structures across species. Among commonly used transplantation models, the baboon best represents the size and spatial distribution of the human caudate and the putamen. Images are printed with permissions from the following agencies: Mouse (Lein et al., 2007; Allen Mouse Brain Atlas, 2015), Marmoset (Yuasa et al., 2010), Rhesus (Mikula, 2013), baboon (Davis and Huffman, 1968), human (adapted with permission from http://www.brains.rad.msu.edu, and http://brainmuseum.org, supported by the US National Science Foundation; (Sudheimer et al., n.d.).

extrastriatal structures such as the GPe, GPi, STN, the nucleus accumbens, and the substantia nigra pars reticulata are all deprived of dopamine in patients with PD (Hornykiewicz, 1998). Thus, PD-mediated dopamine depletion may have effects outside the striatum. However, the capacity for animals models to recapitulate extrastriatal deficits remains a debate (Jan et al., 2000). While, rhesus macaques have shown a significant increase in burst firing from the neurons in the GPi (Wichmann et al., 1999) and STN (Galvan et al., 2014) as a result of dopamine depletion, both rhesus macaques and rodents counterintuitively failed to show a significant change in firing activity in the GPe (Hadipour-Niktarash et al., 2012). The lack of response to MPTP in the rhesus GPe is corroborated by previous studies demonstrating that

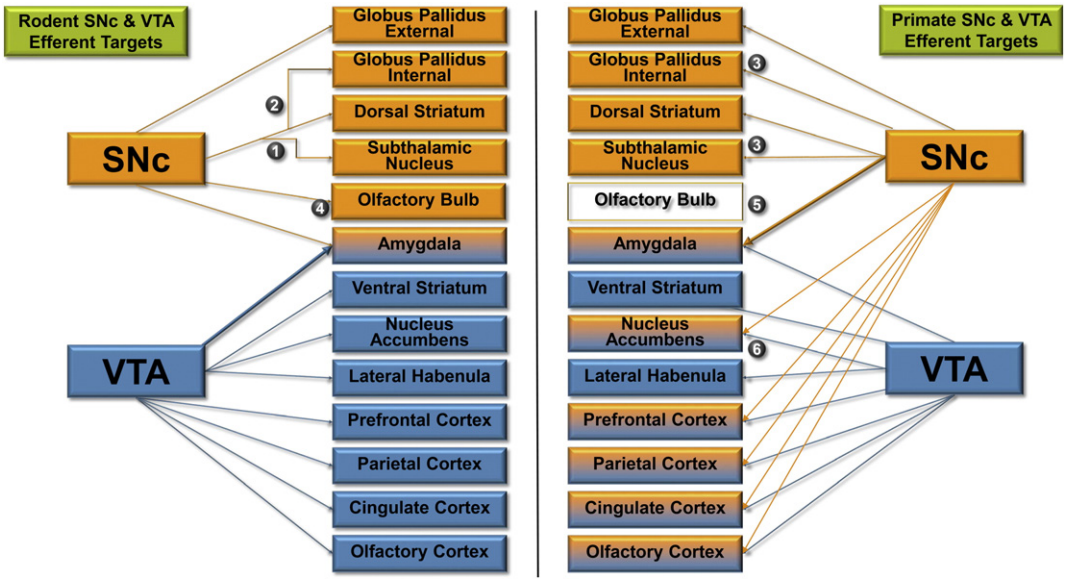

Fig. 2. Efferent targets of SNc and VTA dopamine neurons in the rodent and primate. A chart that compares neuroanatomical connections discovered in mice and rats (rodents), and compares it to connections discovered in nonhuman primates and humans (primates). Nigral projections to the subthalamic nucleus (1) and globus pallidus internal (2) arise from nigralstriatal collaterals in the rodent. The primate SNc contains neurons that project dedicated fibers to these nuclei (3). In the rodent, there exists a nigral efferent that projects directly to the olfactory bulb (4). This pathway has yet to be found in nonhuman primates or humans (5). In the rodent, dopaminergic innervation of the amygdala originates primarily in the VTA (thick blue arrow), whereas in primates, the amygdala receives dopaminergic input primarily from the SNc (thick orange arrow). The primate SNc also sends dopaminergic innervation to the nucleus accumbens (6) and to the frontal cortex (7), however, these pathways are minimal or absent in the rodent.

dopaminergic innervation of the GPe remains intact in MPTP treated rhesus monkeys (Parent et al., 1990; Schneider and Dacko, 1991). The firing rates of extrastriatal neurons in MPTP-treated baboons have not been interrogated, however, MPTP-treated baboons do demonstrate a loss of TH^+ fibers in extrastriatal structures such as the GPe (Varastet et al., 1994), suggesting that they may better model the parkinsonian state than do rodents or rhesus macaques.

2.3. SNc afferents and action potential behavior in rodents

Dopamine neurons receive excitatory glutamatergic input from the subthalamic nucleus, the pedunculopontine nucleus, and the neocortex, as well as inhibitory GABAergic inputs from the substantia nigra pars reticulata, the striatum, and the globus pallidus (Lobb et al., 2011). In humans (Ramayya et al., 2014), NHPs (Bayer et al., 2007), and rodents (Grace and Bunney, 1984a, 1984b), midbrain dopamine neurons are capable of displaying at least two modes of action potential behavior: tonic firing at 2–10 Hz, or burst (high frequency action potential activity) firing at >12.5 Hz. Rhythmic activity results in tonic dopamine release, and this steady-state dopamine tone is believed to establish sensitivity to the phasic dopamine release that occurs during burst firing (Grace, 1991). Burst firing, on the other hand, occurs when a dopamine neuron fires a cluster of action potentials in short proximity. The result is a short-term (phasic) increase in the amount of dopamine release per action potential (Gonon, 1988). The firing rate for optimal dopamine release is species dependent. Dopamine cells in the rat release the highest amount of dopamine when firing at 14 Hz (Gonon, 1988), and these neurons usually do not fire faster than 15 Hz (Grace and Bunney, 1984a, 1984b). Further, electrophysiological experiments carried out on rodent slice preparations in vitro, in which a substantial portion of the SNc's afferents are lost, demonstrated that midbrain dopamine neurons require these afferents to produce burst activity (Grace and Onn, 1989). The fact that dopamine cells depend on afferent activity in order to burst suggests it is possible that species differences in firing properties of dopamine neurons is a result of contrasting hodological profiles.

Differences in burst firing properties, efferent connections, and afferent connections may result in species differences in the type of signals SNc neurons are capable of encoding. Therefore, species differences in the types of behaviors that illicit a burst in dopamine cells may be emergent properties arising from corresponding species differences in efferent and afferent signaling. For example, in the rodent, dopamine neurons in only the VTA will burst when an aversive stimulus is presented (Brischoux et al., 2009; Lammel et al., 2011), whereas in primates, both the VTA and the SNc contain dopamine neurons that may burst in response to aversive stimuli (Matsumoto and Hikosaka, 2009; Pignatelli and Bonci, 2015; Lammel et al., 2011; Jensen et al., 2003; Seymour et al., 2004).

2.4. SNc afferents and action potential behavior in NHPs and humans

Dopamine neurons in primates differ somewhat from those of rodents in burst frequency and in the type of stimuli that illicit a burst. Dopamine neurons of the new world primate, *Callithri jacchus* (marmoset), release a maximal amount of dopamine in the striatum when firing at 20 Hz (Cragg et al., 2000) or almost 1.5× higher than the rates observed in rodents. Burst firing in the old world monkey, *Macaca mulatta* (rhesus macaque), is even higher and has been measured as high as 36 Hz with mean burst rates of approximately 22 Hz (Bayer et al., 2007; Matsumoto and Hikosaka, 2009; Hong and Hikosaka, 2014; Schultz, 1986; Schultz and Aebischer, 1983). The only study to measure burst frequency in the human SNc reported a frequency of 16 Hz (Ramayya et al., 2014), however, these data were obtained from a patient with late-stage PD and it is unknown how PD affects the burst frequency of dopamine neurons in humans. Nevertheless, it is clear that SNc dopamine neurons show species-dependent firing properties that may be a consequence of their particular sets of afferents.

2.5. The source of dopamine release after a reward prediction error in rodents

Dopamine neurons will also burst when an individual is presented with a conditioned stimulus that has been paired with a reward; and dopamine neurons will pause activity if that conditioned stimulus is delivered with no accompanying reward (reward prediction error; RPE) (Schultz, 1997, 1998). This RPE signal is significantly curtailed in rodent models of PD (Pessiglione et al., 2006). However, if the parkinsonian rodent is administered dopamine agonists or L-dopa, which are the most common treatments in PD, the RPE response is significantly protracted (Pessiglione et al., 2006). This observed disruption in reward encoding in rodent models of PD may have clinical significance in that it has been offered as an explanation for why humans with PD experience symptoms such as anhedonia (presumably from reduced RPE signaling) (Loas et al., 2012) and dopamine agonist-induced side effects, such as gambling addiction and hypersexuality (presumably from augmented RPE signaling) (Moore et al., 2014). However, RPE signal itself has not been investigated in MPTP treated NHPs nor in humans with PD.

NHPs offer an advantage over rodents in this type of research because there exist striking neuroanatomical similarities between NHPs and humans in specific areas of the brain that are responsible for responding to reward, such as the prefrontal cortex (Uylings et al., 2003). Specifically, in baboons, complex cognitive functions and their neuroanatomical substrates can be modelled and have demonstrated to be highly reflective of humans in numerous tests (Zurcher et al., 2010). Such functions associated with higher level frontal processing are demonstrably close to those of humans. Relevant cognitive processes include the processing of orthographic symbols (reading English words) (Grainger et al., 2012), analogical reasoning (Fagot and Thompson, 2011), language processing (Medam and Fagot, 2016), and cross-sensory modal integration (Martin-Malivel and Fagot, 2001). It must be noted that these studies did not specifically study reward processing, nevertheless they bolster the notion that high level cognitive processes, such as reward processing, may be more conserved among baboons and humans than they are disparate.

Rodent studies using fast scan cyclic voltammetry to measure the amount of dopamine released as a function of positive RPE (when the reward was greater than expected) and negative RPE (when the reward was less than expected) demonstrated that dopamine release in the nucleus accumbens correlated with magnitudes of the RPE (Hart et al., 2014). In the rodent, the nucleus accumbens receives dopamine input primarily from the VTA, indicating the rodent VTA is capable of signaling both positive and negative RPE in the nucleus accumbens, but such functional organization may not be true in primates (Section 2.6).

2.6. The source of dopamine release after a reward prediction error in NHPs and humans

In 2007, Bayer and Glimcher found that in NHPs, both the frequency and duration of bursts in the SNc correlated with the magnitude of positive RPE, and that the duration of SNc cell pauses correlated with the magnitude of negative RPE (Bayer et al., 2007). Although the nucleus accumbens of both NHPs and rodents displayed a change in dopamine release during RPE, in the rodent this dopamine release is due solely to the VTA neurons while in the NHP this dopamine release is dependent on both VTA and SNc dopamine neurons (Fig. 2), and SNc firing activity correlates with negative RPE while VTA activity correlates with positive RPE (Bayer et al., 2007) (Table 1).

This species-specific difference in the source of the RPE signal to the nucleus accumbens may also extend to humans. Functional magnetic resonance imaging studies demonstrated that the human nucleus accumbens also encodes positive and negative RPE. VTA neurons also

displayed RPE-modulated activity, but only in response to positive RPE and not to negative RPE (D'Ardenne et al., 2008). Thus, it is likely that the signaling for negative RPE in the human nucleus accumbens is performed by the SNc as it is in NHPs, but this has not been directly demonstrated, as the role of the SNc in negative RPE has not been directly investigated in humans.

2.7. Homotopic transplantation into the SNc

A putative solution to problems associated with heterotopic grafts could be to transplant new dopamine neurons into the SNc rather than into the striatum. It has been demonstrated that dopamine neurons grafted homotopically into the SNc will successfully innervate the striatum in the adult rodent brain (Thompson et al., 2009; Grealish et al., 2010; Mendez et al., 2005; Gaillard et al., 2009). However, rodent brain volumes are much smaller and contain disproportionately fewer white matter tracts than those of humans or NHPs (Table 1). Thus, studies are needed to explore the efficacy and viability of homotopic SNc transplantations in models that better represent the human brain. NHPs provide an ideal resource for such studies in that not only are their brain volumes (especially those of baboons) more similar to humans, but the specific structural organization and size of the basal ganglia in NHP brains is particularly homologous to that of humans (Hardman et al., 2002) (Fig. 1). Collectively, the capacity to predict the behavioral deficits of PD-induced lesions in the SNc, and the potential amelioration of deficits following transplantation of new dopamine neurons is likely to be difficult due to disparities in the relevant neuroanatomy and patterns of response to environmental stimuli. As NHPs provide the most accurate model of the human brain in these respects, they represent the model that promises to yield maximally informative and translatable preclinical data.

Of the commonly used laboratory old world primates (rhesus macaque, green monkey, baboon), the baboon displays the greatest similarity to the human in overall brain size (Herculano-Houzel, 2009), glucose metabolism (Herculano-Houzel, 2011), and ratio of gray matter-to-white matter (Schoenemann et al., 2005; Zhang and Sejnowski, 2000; James et al., 1969; Leonard et al., 2008) (Table 1). Importantly for development of PD therapies, the baboon SNc and other regions of the basal ganglia are more similar to those in the human brain in both size (Hardman et al., 2002) (Fig. 1) and density of TH^+ neurons (Table 1) (Bjorklund and Dunnett, 2007) than are those of other NHPs including rhesus macaques and marmosets. The baboon cerebral vasculature also more closely resembles that of the human than does that of macaques (D'Ambrosio et al., 2000; Thomas et al., 1993). For example, the occipital/marginal venous system is present in baboons and humans, but not in rhesus macaques (Aurboonyawat et al., 2007). These similar neuroanatomical features render the baboon a particularly relevant model for optimizing the surgical protocols employed for stem cell therapies for PD.

3. The NHP model for transplantation therapy: immunological considerations

iPS cells can be generated from any individual at any age, thus facilitating the availability of "patient-specific" iPS cell lines that should be immunogenetically matched to the individual from which they were derived (Takahashi et al., 2007; Hargus et al., 2010). However, the degree of immunogenicity of differentiated derivatives of iPS cells upon transplantation back into the individual from whom they were initially derived remains a question (Bjorklund and Kordower, 2013; Morizane et al., 2013; Guha et al., 2013; Araki et al., 2013; Zhao et al., 2011; Mizukami et al., 2014; Lee et al., 2013; Kim, 2011; Lindvall et al., 2012; Parmar and Bjorklund, 2012). For example, previous work in *Macaca fasicularis* demonstrated that an autologous graft can survive transplantation into a NHP brain (Morizane et al., 2013; Wang et al., 2015), and provided proof-of-concept that patient-specific neurons can be produced for the purposes of autologous transplantation therapy in patients with PD. However, in another study, only one of three *Macaca fasicularis* monkeys that had received an autologous graft showed a significant reduction in lesion-associated motor deficits (Hallett et al., 2015), and therefore this aspect of a proposed stem cell-based approach to the treatment of PD or any other disease should be further tested in NHPs. In this section, we review the relevant immunological characteristics of rodents, new world primates, and old world primates as they relate to humans. We pay particular attention to the response to acute inflammatory insults and cyclosporin A (3.1), the homology in sequence and function of the MHCs (3.2 and 3.3), and the effects of aging on the immune system (3.4).

3.1. Immunological considerations: disparities between rodents and humans

While rodents and humans share a great deal of similarity in the organization of the immune system (Haley, 2003; Bailey et al., 2013; Cho et al., 2015; Plackett et al., 2003; Gelinas and McLaurin, 2005; Ferrari et al., 2001), a growing body of literature suggests that immune systems of rodents and humans differ in ways that significantly hamper translation of results obtained in preclinical trials in rodents to successful therapeutics in humans (Renshaw et al., 2002; Boehmer et al., 2004; Rhoades and Orne, 1998; Swift et al., 2001; Rammos et al., 2014; Wang et al., 2014; Bruhns, 2012; Rousseaux et al., 1983; Mestas and Hughes, 2004). Rodents and humans respond differently to infectious agents and possess disparate inflammatory responses (Leist and Hartung, 2013; Tuomela and Lahesmaa, 2013). By 2011, >100 clinical trials testing anti-inflammatory drugs that were effective in rodents had failed in humans (Rice, 2012; Christaki et al., 2011). Typically, <50% of genes shown to be differentially regulated in rodent models of immune response (endotoxemia, trauma, and burn) are found to change expression in humans exposed to the same inflammatory conditions (Seok et al., 2013). When considering the genes that were differentially expressed, the correlation coefficient of the change in expression between the two species was only 0.2 (Seok et al., 2013). Further, mice do not possess the IgA FcαR1 receptor that specifically binds IgA in humans. They also lack homologs to the human FcγRIIA and FcγIIC receptors, which serve to mediate binding of immunoglobulin G isotype 2 (IgG_2) and IgG_3 to neutrophils and ultimately affect susceptibility to infectious and autoimmune diseases in humans (Li et al., 2013; Wolf et al., 2006; van Schie and Wilson, 2000).

Striking immunological distinctions between rodents and humans are observed when microglia are examined. Microglia are the principle mediators of the immune response in the central nervous system (Kreutzber, 1996) and human microglia differ from those of rodents in proliferative capacity, response to TGFβ signaling, expression of TNFγ receptors and histocompatibility complexes (Kreutzber, 1996). Mestas and Hughes (Mestas and Hughes, 2004) have provided a detailed review of the functional differences in immune biology between mice and humans.

Differences in immune function between rodents and NHPs may be reflected in the immune response to tissues grafted for cell-therapies. One study demonstrated a 6% survival rate for iPSC-derived neurons transplanted into the brains of cyclosporin A -treated mice (Kriks et al., 2011). This level of survival is higher than any known iPSC-derived neuron transplantation into NHPs. However, when the same researchers grafted neurons into cyclosporin A-treated rhesus monkeys, they found that the injection sites contained large numbers of Iba1 positive microglia, which was indicative of a potent immune rejection (Kriks et al., 2011). The authors of that study suggested that these primates suffered from persistent inflammation even though the monkeys were immunosuppressed with cyclosporin A (Kriks et al., 2011). These data were corroborated in another study in which a similar pattern of inflammation and rejection of injected cells into cyclosporin A-treated rodents and primates was observed (Gonzalez et al., 2015). These data

highlight the need for additional studies to assess the requirement for- and the proper administration of- immunosuppressants to prevent graft rejections in NHPs.

3.2. Comparative sequence identity of the major histocompatibility complexes among new world primates

The choice of an ideal animal model for studies of transplantation procedures translatable to humans for treatment of PD (or other diseases) depends on several considerations including the comparative organization and sequence identity of the MHCs. Clinical data have confirmed that matching MHC alleles between donor and host greatly mitigates the risk of immune rejection of transplanted cells or organs (Dunn et al., 2011; Rizzari et al., 2011; Vu et al., 2011; Held et al., 1994). As such, MHC matching plays a crucial role in the acceptance or rejection of any transplanted tissues (Magistris et al., 1992; Buus et al., 1987). It follows that it will be preferable to conduct preclinical transplantation studies using animal models that maximally recapitulate the immunogenetic system of humans with respect to organization and sequence variation in the antigen-binding domain of MHCs. To that end, great effort has been directed toward characterizing the MHC proteins of humans and various NHP species (Robinson et al., 2015) including the common marmoset (*Callithrix jacchus*) (de Groot et al., 2012; Antunes et al., 1998), pig-tailed macaque (*Macaca nemestrina*) (Lafont et al., 2014), rhesus macaque (*Macaca mulatta*) (Boyson et al., 1999), olive baboon (*Papio anubis*) (Prillman et al., 1995), yellow baboon (*Papio cyanocephalus*) (Sidebottom et al., 2001), chimpanzee (*Pan troglodyte*) (de Groot et al., 2000; Adams et al., 2000) and others (de Groot et al., 2012). It should be noted here that *Papio cyanocephalus* and *Papio anubis* are both subspecies of the genus *Papio*, and likely possess highly related MHC profiles (Jolly, 1993; Newman et al., 2004; Zinner et al., 2013).

New world primates, such as marmosets, have practical advantages over old world primates as research models, including cost, size and generation time (Ward and Vallender, 2012). However, phylogenetic analyses of MHC class I alleles in new world primates including marmosets and tamarins demonstrate that MHC class I genes cluster in a manner that is distinct from those of old world primates or humans (Adams and Parham, 2001; Watkins et al., 1993), and show an 82% identity with corresponding human leukocyte antigen (HLA; human equivalent of MHC) alleles in humans (Robinson et al., 2015; Cadavid et al., 1997; Shiina et al., 2011). New world primates also demonstrate reduced allelic MHC variability in the antigen binding domains compared to that found in old world primates and humans (Ward and Vallender, 2012; Cadavid et al., 1997; Otting et al., 2002). Further, detailed comparisons have demonstrated that MHC class II families in new world primates are not orthologous to those of old world primates and that these gene families may have evolved independently in new and old world primates (Kriener et al., 2001). Lastly, comparative analyses of the IgG isotypes demonstrated that new world monkey IgG subclasses cannot be distinguished based on their binding to isotypic antigens that are capable of distinguishing human, hominidea, and baboon IgG subclasses, suggesting that IgGs from new world monkeys are structurally different from those of humans and baboons (Gaarder and Natvig, 1974). Thus, significant differences in the organization and function of genes encoding MHC proteins and IgG isotypes in new world primates render these species less accurate models for testing potential adverse immunogenetic responses to transplanted cells used in a cell based therapeutic treatment for PD in humans.

3.3. Comparative sequence identity and functionality of the major histocompatibility complexes (MHC) and immunoglobulins among old world primates

Rhesus macaques and baboons both share a high degree of sequence similarity with humans, but do not have MHC-C loci (Messaoudi et al., 2011; Moffett and Loke, 2006; Prillman et al., 1996). Depending on the specific allele, rhesus macaques share an 80%–99% sequence identity with humans at the HLA loci (Doerks et al., 2002). The baboon genome is 90% homologous to the human genome at loci encoding MHC antigens, while the regions for termini and the T-cell receptor binding sites are nearly 99% homologous with the corresponding regions in the human genome (Prillman et al., 1995). Also, unlike new world monkeys, old world monkeys all express at least one HLA-A homologue, at least one HLA-B homologue and a third HLA-A, -B, or -C homologue, demonstrating conservation in the expression of MHC alleles between humans and old world monkeys (Kennedy et al., 1997). However, the rhesus macaque is the animal model of choice for AIDS-related research in the United States, and macaques with the MHC class I allele, *mamuA**01, are preferred because the reagents for such studies are readily available. Thus, many rhesus macaques are bred to carry this allele specifically, resulting in a reduced level of genetic heterogeneity at the MHC class I loci compared to macaques found in the wild (Kennedy et al., 1997; Viray et al., 2001).

Rhesus macaques lack IgG_3 (Shearer et al., 1999a; Calvas et al., 1999; Martin, 1982), which shows the greatest degree of polymorphism (de Lange, 1989), the strongest response to antigens at low concentrations, and serves to activate the complement system (Michaelsen et al., 2009) in humans. Additionally, macaque IgG_1, IgG_2, and IgG_4 show a lower (~83%) sequence homology at the amino acid level with the respective human homologs than do the corresponding baboon IgGs (Calvas et al., 1999). The baboon on the other hand, possesses all four IgG subclasses, and these subclasses can be functionally identified by interaction with the same isotypic antigens that characterize the IgG subclasses of the human immune system (Gaarder and Natvig, 1974; Attanasio et al., 2002; Damian et al., 1971). Further, the IgG subclasses share 87–90% sequence identity with their human counterparts (depending on the isotype) at the amino acid level (Attanasio et al., 2002; Scinicariello et al., 2002), and the immunoglobulin subclasses also share similar functionality in baboons and humans. For example, in both species, IgG_1 dominates the response to hepatitis B vaccination (Shearer et al., 1999b) and Haemophilus influenza type B polysaccharide vaccination (Shearer et al., 1997). The baboon also proved to be an effective model for West Nile Virus, for which IgG and IgM are the primary mediators of clearance in both humans and baboons, but not in macaques, which are not susceptible to West Nile Disease (Wolf et al., 2006). Macaques are also not susceptible to *Bordetella pertussis* infections, perhaps due to an elevated body temperature (38.7–39.8 °C) compared to that of humans (37 °C). Baboons have a body temperature (37.0–39.0 °C) closer to that of humans, and have proven to be excellent models for studies involving *Bordetella pertussis* (Merkel and Halperin, 2014; Fernandez, 2012).

3.4. The aging immune system

Therapies for neurodegenerative diseases are often additionally complicated by the fact that patients receiving such therapies are advanced in age. Patients >60 years old have a lower risk of acute graft rejection than younger patients (reviewed in Tullius and Milford (2015), but have a significantly increased risk of chronic graft failure and immunosuppressant-induced nephrotoxicity (Heinbokel et al., 2013; Martins et al., 2005). This may be because the immune system of aged patients is different from that of younger patients in several ways. Aged humans demonstrate increased autoantibody production and autoinflammatory response (Rowley et al., 1968) such that it is possible aged patients may elicit a substantially different immune response to transplanted cells than younger patients, even when autologous, patient-specific iPS-derived cells are used. Patients aged 65 and older have increased levels of proinflammatory cytokines such as C reactive peptide (CRP), IL-6 (Harris et al., 1999), IL-8 (Mariani et al., 2002), IL-1, IL-10, and TNF-α (Rink et al., 1998; Brüünsgaard and Pedersen, 2003). Humans also demonstrate an age-related decrease in anti-inflammatory cytokines, such as TGF-ß1 (Okamoto et al., 2005) and DHEA (Hazeldine et al., 2010)

(Table 1). The exact reason for increased chronic rejection in aged graft recipients is unknown, but the aforementioned changes in cytokine levels have been suggested to play a role (Martins et al., 2005). Further, immune senescence is particularly relevant in the case of PD as the high level of reactive oxygen species associated with PD is known to exacerbate age-related increases in inflammatory cytokine production via NFκB signaling (Gloire et al., 2006).

In the common marmoset (a new world monkey), neither CRP nor IL-8 levels vary with age (Tardif et al., 2011), and the relationship between age and the expression of other critical inflammatory cytokines, such as IL-6 and IL-10, is unknown. In the rhesus macaque, the aging immune system is ostensibly concordant with that of humans. Aging rhesus macaques demonstrate increasing levels of IL-10, which is similar to humans, but unlike humans, rhesus macaques do not show age-related increases in IL-1, IL-6, or TNF-α (Mascarucci et al., 2001). Conversely, rhesus macaques display an age-related decline in IL-6 and TNF-α (Asquith et al., 2012), a pattern that is opposite of that observed in aging humans (Table 1). Aged baboons do demonstrate increased production of autoantibodies (Attanasio et al., 2001), IL-6, and CRP (McFarlane et al., 2011), in a manner similar to humans, but not IL-10 (McFarlane et al., 2011). Also as in the human, levels of TGFβ1 and DHEA decrease as a function of aging in the baboon (Willis et al., 2014) (Table 1), whereas these changes are not known to take place in rhesus, suggesting that results discovered in cell transplantation studies involving aged baboons will more accurately predict the extent of immune reactions to cell grafts in aged humans. Species differences in cytokine regulation, and their impact on clinical experimentation was illustrated in the preclinical testing of TGN1412, an anti-CD28 antibody designed to suppress immune response independently of CTLA-4. While TGN1412 showed successful results in preclinical trials in the rodent and rhesus macaque, administration to humans in phase I clinical trials resulted in a cytokine storm and cytokine release syndrome (Suntharalingam et al., 2006). Later investigations found that this was due to effector memory T-cells that are activated by CD28 antibodies in humans, but not in rhesus macaques. This is because effector memory T-cells in rhesus do not express the appropriate receptor for CD28. Experiments on TGN1412 in the baboon, however, were later able to recapitulate the results found in humans (Poirier et al., 2014), and since then, the baboon has been the NHP model of choice for immunotherapy experimentation (Poirier et al., 2016).

Finally, the baboon has also been used heavily for preclinical drug trials because the activity of the blood brain barrier transport protein, P-glycoprotein, is highly reflective of that in humans (Chu et al., 2013; Syvanen et al., 2009). Because of this and the similarities between the baboon and human immune systems noted above (Table 1), psychopharmacological studies of blood brain barrier penetrance in baboons (Blin et al., 1988; Villemagne et al., 1998) have been shown to be predictive of outcomes of the same psychopharmacological treatments in humans even where other NHPs have failed to adequately predict human outcomes (Hou et al., 2014; Volkow et al., 2001; Ding et al., 1997; Volkow et al., 1998). The combination of these features renders the baboon a particularly useful model for studies investigating immunosuppressive regimens for the tolerance of cell grafts designed to treat neurodegenerative diseases such as PD.

4. Nonhuman primate models for transplantation therapy: motor and non-motor manifestations of the MPTP lesion

Methods that have been used to induce a parkinsonian state in NHPs include 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) administration (Emborg, 2007), 6-hydroxydopamine administration (Ungerstedt, 1968), and transduction with viral vectors to promote expression of specific proteins such as alpha synuclein (Orth et al., 2003; Decressac et al., 2011). Compared to other lesion-based models of PD including rotenone, paraquat, and 6-hydoxydopamine (Tanner et al., 2011), systemic administration of MPTP is most directly linked to human PD and the most common method to phenocopy PD in animal models (Langston et al., 1983; Langston, 1985). MPTP metabolites are taken up by dopamine neurons via the dopamine transporter and then function as an inhibitor to complex I of the mitochondrial respiratory chain in these cells (Schapira et al., 1989). For reasons that remain undetermined, dopamine neurons from the SNc are especially vulnerable to MPTP (Hantraye et al., 1993; Johannessen et al., 1985; German et al., 1992). Thus, the result of MPTP treatment is a neurodegenerative state that is similar to PD. In this section we review the consequences of MPTP induced lesions in rodents (4.1) and NHPs (4.2), including manifestation of both motor and non-motor symptoms.

4.1. Motor and non-motor manifestations of the MPTP lesion in rodents

Mice and rats are significantly less sensitive to the deleterious effects of MPTP than primates and humans (Muthane et al., 1994; Dauer and Przedborski, 2003). To obtain the full range of neuronal deficits observed in NHPs, mice require dosages reported to be as high as 30 mg/kg/day (cumulative dose of 300 mg/kg) (Johannessen et al., 1985; Seniuk et al., 1990). Thus, at doses much higher than those administered to primates, midbrain dopamine cells can also be lesioned in the rodent with MPTP (Bannon et al., 2015), resulting in motor deficits. Assays of motor deficits in MPTP-lesioned rodents are robust in tests of gross motor movement, such as walking a balance beam (Sharma and Deshmukh, 2015) or running on an exercise wheel (Sconce et al., 2015) (Table 1). However, resolving symptoms of PD such as resting tremor and bradykinesia have proven more difficult in rodents, and studies have produced conflicting results about whether or not such deficits exist in MPTP treated rodents (Sedelis et al., 2001a,b; Salamone et al., 1998; Ferro et al., 2005).

4.2. Motor and non-motor manifestations of the MPTP lesion in new world and old world monkeys

MPTP has been used to create PD-like symptoms in many NHPs, including the squirrel monkey (Di Monte et al., 2001), common marmoset (Kupsch et al., 2001), cynomolgus monkey (Brownell et al., 1998), rhesus macaque (Wichmann et al., 1999), and olive baboon (Hantraye et al., 1993; Varastet et al., 1994). Although the particular dosage administered to an animal depends on the route of administration and the experimental design (acute or chronic lesion), MPTP dosages for NHPs are typically reported at 3 mg/kg/day (cumulative dose of 15–30 mg/kg) in marmosets (Rose et al., 1993), 3 mg/kg/day in squirrel monkeys (Forno et al., 1986), 1.2 mg/kg/day (cumulative dose of 1.2–7.8 mg/kg) in rhesus macaques (Johannessen et al., 1985; Ovadia et al., 1995; Fifel et al., 2014), and 0.1 mg/kg/day (cumulative dose of 11–40 mg/kg) in the baboon (Varastet et al., 1994; Hantraye et al., 1993). There are only three reported cases of MPTP exposure in humans, and the dosages could not be determined absolutely, but estimates suggest that cumulative dosages of 6–12 mg/kg were sufficient to induce permanent neuronal degeneration in the SNc of humans (Langston et al., 1999). These values are much lower than those reported for rodents, and the differential susceptibility to MPTP seen in rodents and primates may be due to differential metabolism of MPTP (Johannessen et al., 1985), lower expression of specific dopamine transporters that transport MPTP in rodents (Shimohama et al., 2003), differential cellular composition of the SNc in rodents and primates (Muthane et al., 1994), and/or the fact that midbrain dopamine cells of the rodent do not contain the pigment, neuromelanin, which is found in primate dopamine cells and enhances the toxicity of MPTP (Herrero et al., 1993). NHP models are advantageous in that their long life spans allow for chronic administration of low-doses of MPTP, which better reflects the chronic pathogenesis of PD in humans (Hantraye et al., 1993; Smith et al., 1992; Bezard et al., 1997; Meissner et al., 2003). Similar to humans suffering from PD, NHP MPTP models demonstrate cognitive deficits (Schneider and Pope-Coleman, 1995;

Schneider and Kovelowski, 1990; Schneider and Roeltgen, 1993; Roeltgen and Schneider, 1994) and loss of dopamine neuron innervation in extrastriatal targets such as the globus pallidus (Jan et al., 2000) and the prefrontal cortex (Brozoski et al., 1979; Aron Badin et al., 2015) – symptoms that are not observed in rodent models (see above Sections 2.1 and 2.2) (Table 1).

Specifically in baboons, chronic administration of MPTP induces a selective destruction of dopaminergic neurons in the caudal and ventrolateral regions of the SNc (Varastet et al., 1994), a pattern that has otherwise only been noted in cases of human PD (Kish et al., 1988). Similar to both marmosets and rhesus, baboons also demonstrate the full range of symptoms associated with parkinsonism including rigidity, resting tremor, bradykinesia (Hantraye et al., 1996; Viallet et al., 1981), postural instability (Hantraye et al., 1993; Drouot et al., 2004), and aggregation of alpha synuclein (Kowall et al., 2000).

As noted above (Section 1), victims of PD suffer from non-motor symptoms such as cognitive impairment (Litvan et al., 2012), depression, fatigue, and sleep disorders (Chaudhuri and Schapira, 2009) that are not observed in MPTP treated mice (Laloux et al., 2008). Despite the fact that non-motor symptoms of PD have been observed as early as 1975 (Ansari and Johnson, 1975), they have only recently begun to receive attention in the scientific community (Shulman et al., 2002; Goetz et al., 2003). For example, clinical assessment of non-motor symptoms was not added to the Unified Parkinson's Disease Rating Scale until 2008 (Goetz et al., 2008). As a result, there are currently no studies that investigate the ability of cell-based therapies to treat the non-motor aspects of PD. However, based on the fact that NHP models of PD and humans with PD present with non-motor symptoms that are absent in rodent models of PD (Table 1), future studies aiming to test the ability of cell-based therapies to treat non-motor symptoms should be carried out in NHPs. MPTP-induced models of PD in NHPs such as the marmoset (Collins et al., 2000) and rhesus (Fifel et al., 2014; Schneider and Pope-Coleman, 1995; Schneider and Kovelowski, 1990) have demonstrated many of these same non-motor symptoms, including cognitive deficits (Schneider and Roeltgen, 1993; Decamp and Schneider, 2004), activated microglia (Barcia et al., 2004), and disruptions in circadian rhythms (Fifel et al., 2014). Baboons display behavioral and cognitive abilities correlative to those of humans (Fagot and Paleressompoulle, 2009; Goujon and Fagot, 2013), and exhibit cognitive deficits when administered MPTP (Hantraye et al., 1996) (Table 1). Baboons also demonstrate other non-motor Parkinsonian symptoms such as age-related loss of dopamine compensation (Duong, 2010).

5. The baboon as an optimal model for cell-based therapies for PD

In this review, we have presented a detailed comparison of NHP biology with respect to the neuroanatomical, neurophysiological, immunological features pertinent to studying the transplantation of iPSC-derived neurons for treatment of PD. NHPs in general, and baboons in particular, offer considerable advantages over rodents as model systems for preclinical studies to optimize the efficacy and safety of a cell-based approach to the treatment of PD. Among NHPs, old world monkeys are particularly valuable for use in neurological transplantation studies because they share critical neuroanatomical commonalities with humans, including physical separation of the nuclei of the striatum (Bove and Perier, 2012), which is the primary target of SNc neurons, and a gyrencephalic brain (Wu et al., 2012). Old world monkeys also demonstrate age-related loss of TH^+ neurons in the SNc and a correlated decline of motor and cognitive skills (Emborg et al., 1998). These age-related changes are not observed in new world monkeys (McCormack et al., 2004). Of the old world genera, rhesus macaques (*Macaca mulatta*) are the most commonly used NHP species in biomedical research, but are in high demand for HIV/AIDS studies. In contrast, the baboon is widely available and is equally homologous to humans at the genomic level as the rhesus, with both possessing genomes with at least 92% sequence identity to the human genome (Caccone and Powell, 1989; Rogers and Hixson, 1997).

However, the advantages of NHP models are not without costs. Studies using NHPs typically require greater time to complete than those using rodents. With respect to PD, this includes the time needed to create a stable lesion in the primate using MPTP and the time required to observe a stable recovery post-transplantation. For example, injection of 6-hydroxydopamine directly into the rodent SNc can effectively ablate the SNc within 1–3 days (Hokfelt and Ungerstedt, 1973). It is possible to use MPTP to lesion the SNc of a NHP within one week via intracarotid injections (Emborg et al., 2008) or high doses of systemically injected MPTP (Gonzalez et al., 2015). However, such methods often produce unwanted toxicity and highly variable lesions. The use of MPTP to create a stable lesion in NHPs requires administration of low doses over a period of two to three months (Drouot et al., 2004) with regular assessments for a period of six months to a year to ensure there is no spontaneous recovery (Potts et al., 2014). Following cell transplantation into mice, a stable recovery can typically be observed within one month (Gaillard and Jaber, 2011). In NHPs such as the baboon, however, motor activity does not return to baseline until at least six months after transplantation (Hallett et al., 2015). Thus, it could take 14–28 months to observe both a stable lesion-induced motor deficit and a stable graft-mediated recovery in baboons.

Experiments in NHPs can also be more technically challenging than those carried out in rodents. For example, MPTP is a highly toxic reagent and animals exposed to it need to be housed in biosafety level 2 laboratories and cared for by highly trained staff. Further, although a stereotactic atlas does exist for baboon brains (Davis and Huffman, 1968), the presence of variation in brain volumes among baboons (Rogers et al., 2007; Davis and Huffman, 1968) typically requires that precise location of the injection sites should be determined using MRI (Jarraya et al., 2009). Finally, lengthy experiments involving NHPs incur significant financial costs.

However, despite the costs associated with the use of NHPs in biomedical research, preclinical studies using NHP models are necessary to validate the efficacy and safety of novel cell-based therapeutic procedures prior to translation of these approaches to the clinic. Multiple examples now exist of efforts to translate methodology directly from rodent models to the clinic with little or no success (Leist and Hartung, 2013; Rice, 2012; Christaki et al., 2011; Seok et al., 2013; Courtine et al., 2007; Donahue and Dunbar, 2001). While experiments carried out in NHPs are financially costly, they are many times less expensive than clinical trials. Indeed, the costs of such failed efforts to translate protocols directly from rodent models to the clinic can easily *exceed* the costs of well-planned preclinical studies involving NHP models that can significantly enhance the likelihood of successful clinical translation. Thus, efforts to avoid costs by avoiding the use of clinically relevant NHP models to validate the efficacy of cell-based therapies can potentially result in *higher* costs in the long run. And this problem will be magnified exponentially if a protocol developed in rodent models and translated directly to the clinic leads to unwanted off-target effects that may accrue uniquely in primates – such as the induction of tumorigenesis.

Rodent models and models involving other smaller mammals (e.g. rabbits or pigs) afford significant experimental power both in terms of the number of replicate animals that can be investigated and the many research models available, especially in the mouse. Thus, the ideal scenario for development of novel stem cell-based therapies for the treatment of PD or other complex diseases will likely involve initial studies in rodent and other small mammal models to develop initial protocols – followed by testing in the more clinically relevant NHP models to validate the efficacy and safety of each protocol and/or to modify the protocol as needed prior to translation to the clinic.

Among NHP models available for studies of cell-based approaches to the treatment of PD, we have summarized the advantages of the baboon. The baboon was the first NHP for which a detailed genetic linkage

map was generated (Cox et al., 2013), and the baboon genome is now largely complete and available (https://www.hgsc.bcm.edu/baboon-genome-project-0). The Southwest National Primate Research Center currently houses baboons with well documented pedigrees spanning eight or more generations, with genotyping data and banked biomaterials that represent a unique resource for tracing heritable contributions to disease progression. These assets will facilitate genetic studies to define the extent of relatedness among donors and recipients required for successful cell-based therapeutic approaches, as well as studies at the genomic level to further confirm the functionality of cells prior to and following transplantation. Taken together, the many advantages described in this review establish NHPs in general, and the baboon in particular, as optimal, penultimate preclinical models with which to validate the utility of each specific protocol prior to transitioning that protocol to clinical use.

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